REMARKS

Applicants have amended claim 71 for clarification by specifying that the fluorocarbon core is a liquid fluorocarbon core. This is supported on page 12 of the specification, lines 11-17 and in dependent claims 78 and 79. No new matter has been added and entry of the amendment is respectfully requested.

Applicants appreciate the withdrawal of the rejection under 35 U.S.C. § 103 previously made. The only outstanding rejections are based on citations of assertedly anticipatory documents, although the rejection over Unger is also characterized as citable under § 103 in the alternative.

The Rejection for Anticipation Over the Lanza Patents

Claims 71-79 and 82-86 were rejected as anticipated by any of U.S. 6,690,907 ('907); 5,780,010; or 5,958,371 (the Lanza Patents) as assertedly evidenced by U.S. 4,595,680 ('680); 5,656,287 ('287); or 6,149,937 ('937).

The disclosures of the Lanza Patents are substantially similar. The Examiner is correct that Lanza discloses (among other carriers) targeted nanoparticles comprising liquid fluorocarbon cores coated with a lipid/surfactant layer and that Lanza indicates that such particles may include chemotherapeutic agents. What Lanza does not disclose, either inherently or explicitly, is the essential claim limitation that "said drug is contained in said layer and not carried or deposited in the interior of said nanoparticle." The Office has disputed this on two separate grounds.

Combination with '680

First, the Office points out that the outer lipid monolayer of the perfluorocarbon emulsion nanoparticles in Example 2 of the '907 patent contains biotinylated phosphatidyl ethanolamine. In

the view of the Office, the nanoparticles of this example meet this limitation because, according to the Office, the '680 patent indicates that "phosphatidyl ethanolamine can be considered to be a drug having activity against disorders related to the central nervous system."

First, there is no disclosure in '680 that biotinylated phosphatidyl ethanolamine has any pharmacological activity. It is entirely unproven and never suggested in the cited art that biotinylated phosphatidyl ethanolamine would have any biological activity at all. There is no evidence of record with respect to this compound.*

Perhaps more important, the '680 patent does not describe phosphatidyl ethanolamine itself as having activity with respect to central nervous system disorders. Rather, the phosphatidyl ethanolamine is an excipient for the administration of the active ingredient, which is phosphatidyl serine. The pharmacological activity of phosphatidyl serine is extensively discussed in the '680 patent at column 3, line 36-column 5, line 14. The only activity stated to be associated with phosphatidyl ethanolamine is coagulant activity, as set forth in column 3, line 17. It is presumably this coagulant activity that is included in the compositions described in '680 to offset side effects of the active ingredient, phosphatidyl serine. It is phosphatidyl serine that is the drug to be delivered, not phosphatidyl ethanolamine.

* There are two caveats with regard to this – first, it is noted that Example 2 also includes control fluorocarbon nanoparticles where the phosphatidyl ethanolamine is not biotinylated, but it is never suggested that these be used for drug delivery since they have no mechanism for targeting. All of the examples in the Lanza patents cited employ biotinylated phosphatidyl ethanolamine for *in vivo* administration. Second, applicants note that U.S. 6,548,046 does contain examples where the phosphatidyl ethanolamine is not biotinylated but the particles are, nevertheless, targeted – in this case, the phosphatidyl ethanolamine is derivatized to alternative moieties, and is thus not phosphatidyl ethanolamine *per se*. This document would be citable only under 35 U.S.C. § 102(e) as it did not issue until 15 April 2003 and has an application date of 24 September 1999. As the inventors of the '046 patent are the same as those in the present application, however, it cannot validly be cited under this statutory section.

It is clear from a reading of Lanza that biotinylated phosphatidyl ethanolamine is not being delivered as a drug, but rather as a part of what *could be* a delivery system for a drug. If the Office interprets even phosphatidyl ethanolamine itself to be a drug, it is apparent that the presence of a drug in the outer layer of Lanza's particles is not inherent. The expanded definition of a "drug" evidently countenanced by the Office would also apply to the liquid perfluorocarbon *core* of the present nanoparticles since such nanoparticles were the subject of an Investigational New Drug (IND) as oxygen-carriers and blood supplements. It is therefore not inevitable that all "drugs" would be in the outer layers of the present particles. As noted in the previous response, this is a requisite for inherent anticipation. But more sensibly, taken in the context of the present invention, clearly the lipid/surfactant layer cannot itself be considered a "drug."

Applicants appreciate that the Examiner evidently recognizes that this rejection is not applicable to claims 87-93; in applicants' view, it is not applicable to any claims and may properly be withdrawn.

Combination with '287 and '937

The second aspect of this basis for rejection is the combination of the teachings of the Lanza patents with '287 and '937.

Both of these secondary documents concern liposomes.

The portion of the '937 patent cited is column 1, lines 53-67, which states that hydrophilic compounds are entrapped within the inner aqueous compartments of phospholipid vesicles and lipid-soluble drugs are almost completely trapped inside the lipid layers which encircle the aqueous compartments. The '287 patent is cited as having relevant disclosure in column 2, lines 31-54, which states substantially the same thing.

Applicants are certain that the Office recognizes the distinction between liposomes which contain aqueous internal portions surrounded by lipid bilayers and the fluorocarbon nanoparticles of the invention which comprise liquid fluorocarbon surrounded by a lipid/surfactant layer, generally suspended in a aqueous medium. There is no hydrophilic portion of the nanoparticles of the invention themselves, only the continuous aqueous medium in which they are suspended.

However, as applicants understand the position of the Office from the discussion at the interview, it is simply that these patents directed to liposomes demonstrate that "like will seek like" and that hydrophobic drugs will inhabit hydrophobic portions of compositions and hydrophilic drugs will inhabit hydrophilic portions thereof. Applicants do not question this. However, as will be evident from the following discussion, by practicing the teachings of the present application, either hydrophilic or hydrophobic drugs may be incorporated successfully into the lipid/surfactant layer of the invention nanoparticles, and, unlike liposomes, there is no hydrophilic region integral to the particles themselves – the only hydrophilic region is the contiguous aqueous medium external to the particles.

The Office then reasons that the Lanza patents mention doxorubicin as one of the drugs that might be employed and asserts that doxorubicin is lipophilic and would thus have a tendency to incorporate into the lipid layer of a nanoparticle, because, according to the Office, the nanoparticle system can be considered to be a liposome, quoting line 27 in column 4 of the '287 patent. This line reads: "cyclosporin **(sic)** can be formulated having high entrapment characteristics along with good stability" citing several U.S. patent applications. Why behavior of cyclosporin is cited as defining the behavior of doxorubicin is unclear. It should also be apparent from the quotation of the cited

portion of '287 that no evidence is offered that liposomes and the present nanoparticles are the same.

Doxorubicin, according to The Merck Index entry (copy enclosed), is supplied as the hydrochloride salt which is soluble in water, methanol and aqueous alcohols, but practically insoluble in organic solvents. Thus, according to the reasoning of the Office (and the secondary documents), doxorubicin in liposomes would be entrapped in the interior, rather than in the lipid bilayer. Applicants acknowledge, however, that paclitaxel, also exemplified in the present application is indeed insoluble in aqueous media.

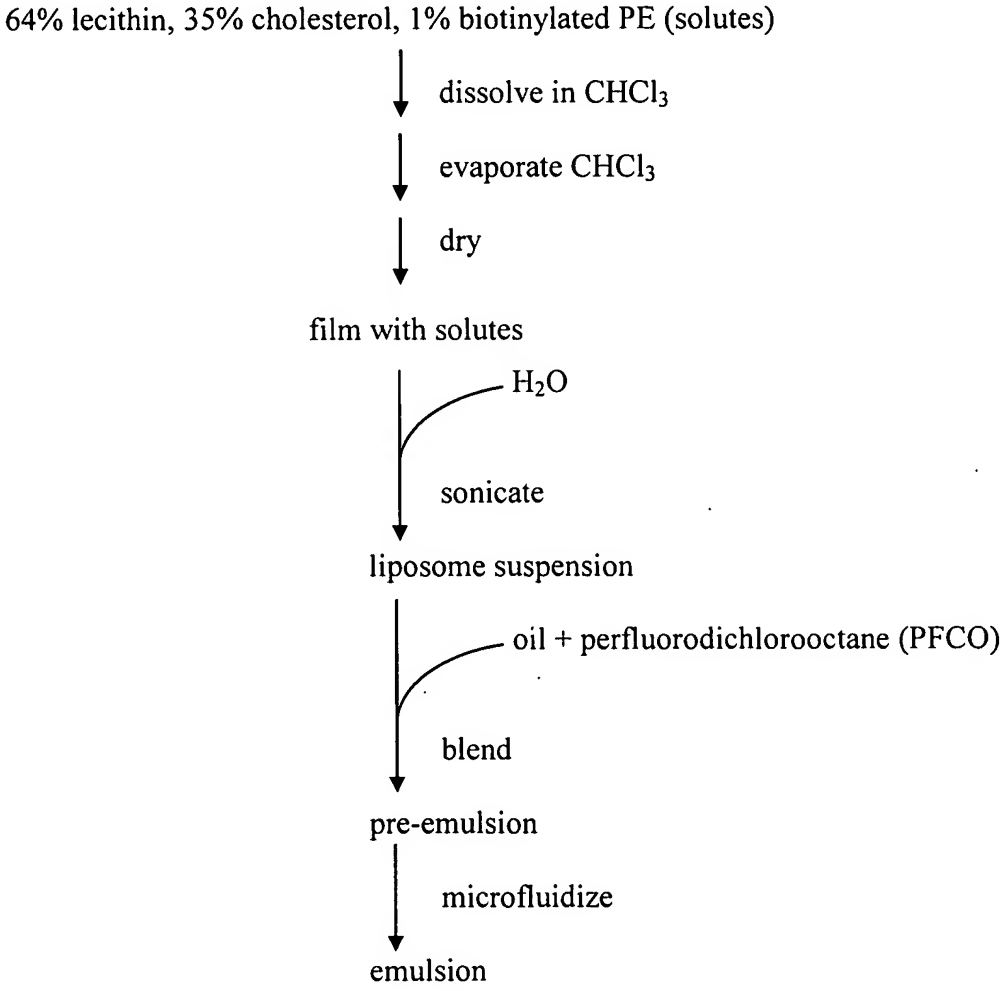
As there is no explicit teaching in the cited Lanza patents that drugs in general would be contained in the lipid/surfactant layer, any anticipation must be inherent. Applicants took some pains in the response to the previous Office action to set forth the case precedent for what is required to find inherency. As stated previously, the Federal Circuit has consistently cited the principle set forth in *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991) which was actually quoted from two earlier CCPA cases – *In re Oelrich*, 666 F2d 578, 212 USPQ 323, (CCPA 1981) which in turn quoted *Hansgirg v. Kemmer,* 40 USPQ 665 (CCPA 1939).

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

Given this standard, Lanza must teach the construction of the nanoparticles containing drugs in such a way that the drug, whether soluble in water or soluble in nonpolar solvents, will inevitably

reside in the lipid/surfactant layer. While applicants agree that the Lanza disclosure generically covers circumstances wherein a drug might so reside, such localization is not the inevitable result of the teaching of Lanza.

Lanza contains only one example that describes a process for preparing fluorocarbon nanoparticles. This is Example 1. The procedure in Example 1 can be diagrammed as follows:



Lanza does not describe any process for including a drug in the emulsion. Thus, drug could be added with the initial mixture, with the water during sonication, or with the oil and PFCO before

blending. Depending on when the drug is added, the drug will or will not be entrapped in the lipid/surfactant layer.

The present application specifically teaches, as shown in Examples 1 and 2, that the drug is added along with the initial ingredients before the chloroform is evaporated and before sonication with water. Thus the drug is included in the solute-containing film formed as shown in the diagram. If this is not done, the drug does not reside in the lipid/surfactant layer.

Thus, the teachings of the cited Lanza patents clearly fail to meet the standard required by law for inherent anticipation. This is comparable to the situation in *Glaxo, Inc. v. Novopharm, Ltd.*, 52 F3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995). This case concerned Zantac®. An initial patent on this molecule described the preparation of what came to be known as Form 1. Glaxo later found that a different polymorphic form, designated Form 2, had superior properties. A later patent was filed and issued on Form 2. In an infringement suit against Novopharm, triggered by Novopharm's Abbreviated New Drug Application (ANDA), paragraph 4 certification, Novopharm asserted that one of the examples in Glaxo's earlier patent resulted in Form 2, and although this was not recognized, there was inherent anticipation. In evaluating the proceedings below, the Federal Circuit noted that Novopharm's expert "performed the process disclosed in Example 32 of the '658 (first) patent thirteen times and each time they made Form 2 crystals, not Form 1 as Glaxo claims."

This, however, was *not* good enough to justify a holding of inherent anticipation:

> But the District Court found that the practice of Example 32 could yield crystals of *either* polymorph. It specifically found that Glaxo's David Cullen originally made Form 1 by practicing Example 32 and that Glaxo's expert, Nicholas Crouch, did so as well.

Based on this evidence, the District Court held that anticipation did not exist, and the Federal Circuit affirmed. Thus, the finding of *lack* of inherency was justified even if there was evidence

that sometimes, *but not always*, Form 2 was obtained by following the directions in the earlier patent. The legal principle behind this affirmation was explicitly stated to be that quoted above from *Continental Can*. It must be apparent that the requirements of the claimed invention must be met by the teachings of the prior art every single time that they are practiced.

Clearly, the criterion for inherent anticipation evidenced by *Glaxo* is not met here. Since the cited Lanza patents provide no instructions as to the point in the process at which the drug must be added, the procedure described in those patents does not inevitably lead to the required result – that the drug resides exclusively in the lipid/surfactant layer. Only in those instances, included, but not required by Lanza, where the drug is added at the appropriate time, as taught by the present application, does this result occur. The same result is observed for both hydrophilic and hydrophobic drugs as evidenced by the enclosed declaration by Dr. Gregory Lanza, one of the inventors herein, which describes experimental results in accordance with this statement.

Thus, applicants believe this rejection is in error and should be withdrawn. It is noted, however, that claims 87-93 are, in any event, free of this aspect of the rejection as well.

The Rejection Over U.S. 2001/0018072 to Unger ('072)

All claims were rejected over this document, including claims 78-79 which specify that the fluorocarbon core is a liquid. This limitation has been made explicit, now, in claim 1. The disclosure of '072 is, on its face, to a "solid" porous matrix not to "liquid" nanoparticles. On this basis alone, the '072 disclosure does not anticipate or render obvious the presently claimed invention.

The only suggestion noted in '072 that the drug be in a lipid/surfactant outer layer (or any outer layer) is said to be in the generic discussion in paragraph 61. The cited paragraph is simply a

definition of "in combination with" or "together with" to include a variety of meanings. These meanings include a multiplicity of possibilities, *e.g.*,

> covalently or non-covalently associated with the matrix or stabilizing materials (last lines on page 5)

or they may be

> integrated within the layers or wall of the matrix or vesicle, for example, by being interspersed among stabilizing materials which form or combine with the vesicles or wall (page 6, lines 4, *et seq.*)

or the drugs may be

> concurrently entrapped within an internal void of the matrix or vesicle and are integrated within the layers of walls of the matrix or vesicles and/or located on the surface of a matrix or vesicle or non-vesicular stabilizing material (lines 12, *et seq.*).

In addition, according to this paragraph,

> the ligand may interact chemically with the walls of the matrix, vesicles, including for example, the inner and outer surfaces of the matrix, vesicle and may remain substantially adhered thereto. (whatever this means, lines 16, *et seq.*).

The Office refers to lines 28-44 which state that the bioactive agent may also "interact with the inner or outer surface of the matrix or vesicle or the non-vesicular stabilizing material in a limited manner."

The further teaching of this paragraph, redacted for comprehensibility so as to apply to vesicles (although '072 is really concerned with matrices) reads as follows:

> Such limited interaction would permit migration of the bioactive agent, for example, from the surface of a first vesicle to the surface of a second vesicle. Alternatively, such limited interaction may permit migration of the bioactive agent, for example, from within the walls of the vesicle to the surface of the vesicle and *vice versa* or from inside a vesicle to within the walls of a vesicle and *vice versa*.

Clearly, the bioactive agent is not contained exclusively in the lipid coating layer of anything, but can move around in all directions.

The content of this paragraph clearly precludes a finding of any kind of inherent anticipation. Such a multiplicity of possibilities is described, that, according to the law cited in the previous response, inherent anticipation cannot possibly be found. Neither can any *suggestion* be found to have a drug "contained in said layer and not carried or deposited in the interior of the nanoparticle." This paragraph in fact teaches away from that limitation since all possibilities are encompassed.

And as to the "limited interaction" described in the cited passage, the ability of the bioactive agent to migrate within the vesicle or from one vesicle to another is inconsistent with the requirement that the drug remain in the outer layer until cell contact is made.

Accordingly, applicants believe this basis for rejection may properly be withdrawn.

Conclusion

The rejection of claims 71-79 and 82-86 as anticipated by the Lanza patents is believed overcome by demonstrating that neither phosphatidyl ethanolamine nor its biotinylated form is a drug to be delivered to tissue, but rather a carrier, and by demonstrating that the secondary documents neither show that the claimed nanoparticles are liposomes nor demonstrate that doxorubicin would be, by its nature, incorporated into the outer layer even of liposomes.

The rejection of claims 71-79 and 82-93 over '072 (Unger) is believed overcome by the explicit limitation that the perfluorocarbon cores of the nanoparticles are liquid in light of the clear description that the teaching of '072 is directed to solid matrices. Further, '072 fails to teach or suggest incorporation of the drug into the outer layer of any nanoparticles to enhance drug delivery.

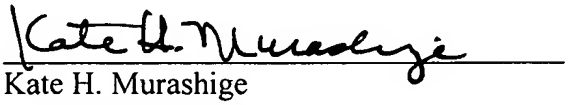
Indeed, '072 does not suggest any particular manner of including drugs in delivery systems in general in order to effect superior delivery, but instead encompasses all possible methods of incorporating drugs into "solid matrices." It is noted that claims 87-93 are rejected only over '072 – there is no other outstanding basis for rejection of these claims.

Accordingly, it is respectfully submitted that the presently pending claims, claims 71-79 and 82-93 are free of the outstanding rejections and passage of these claims to issue is respectfully requested.

Applicants wish to again express their gratitude to Examiners Vanik and Kishore for the helpful interview.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532512000401.

Respectfully submitted,

Dated: October 27, 2006 By: 

Kate H. Murashige
Registration No. 29,959
MORRISON & FOERSTER LLP
12531 High Bluff Drive
Suite 100
San Diego, California 92130-2040
Telephone: (858) 720-5112
Facsimile: (858) 720-5125